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Chromosome 9p21 polymorphism is associated with myocardial infarction but not with clinical outcome in Han Chinese

Wen Hui Peng[1,2], Lin Lu[1,2], Qi Zhang[1], Rui Yan Zhang[1], Ling Jie Wang[2], Xiao Xiang Yan[2], Qiu Jing Chen[2] and Wei Feng Shen[1,2,*]

[1] Department of Cardiology, Rui Jin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China
[2] Institute of Cardiovascular Diseases, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China

Abstract

Background: rs1333049 polymorphism on chromosome 9p21 has been shown to affect susceptibility to coronary artery disease (CAD) in Caucasians. This study examined the association of rs1333049 with myocardial infarction (MI), angiographic severity of CAD and clinical outcome after a first acute MI in Han Chinese.
Methods: rs1333049 polymorphism was genotyped in 520 patients with a first acute MI and in 560 controls. The number of angiographically documented diseased coronary arteries (luminal diameter stenosis $\geq$50%), echocardiographic left ventricular ejection fraction (LVEF), and major adverse cardiac events (MACE) during follow-up (mean, 29$\pm$15 months) were recorded.
Results: Patients with MI had higher frequencies of the *CC* genotype (30.0% vs. 20.7%) or *C* allele (55.5% vs. 46.2%) compared with controls (all $p<0.01$). rs1333049 polymorphism was strongly associated with MI [odds ratio (OR) 1.48, 95% confidence interval (CI) 1.22–1.79] after adjusting for traditional risk factors. Although longer hospitalization stay was observed in patients with the rs1333049-*C* allele, this polymorphism was not related to angiographic severity of CAD, LVEF, and occurrence of MACE after MI.
Conclusions: This study demonstrates an association of rs1333049 polymorphism locus on chromosome 9p21 with risk for MI, but not with post-MI prognosis in Han Chinese.
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Keywords: coronary artery disease (CAD); myocardial infarction (MI); outcome; 9p21; polymorphism.

*Corresponding author: Wei Feng Shen, PhD, MD, Department of Cardiology, Rui Jin Hospital, 197 Rui Jin Road II, Shanghai 200025, P.R. China
Phone: +86-21-64370045, Fax: +86-21-64457177,
E-mail: rjshenweifeng@yahoo.com.cn
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Introduction

It is widely accepted that genetic variation is important for the pathogenesis of coronary artery disease (CAD), myocardial infarction (MI) and clinical outcome (1, 2). Although numerous candidate genes have been implicated in the development and progression of atherosclerosis, the genes that are responsible remain largely unknown. Recently, genome-wide association studies have demonstrated a locus on chromosome 9p21 for CAD susceptibility in Caucasians (3–7). Chromosome 9p21 was found to also be associated with other atherosclerotic diseases such as stroke and aneurysm (8–10).

Studies on chromosome 9p21 were performed primarily in Caucasians, while similar studies in Asians are less common (7). As variants and their frequencies of chromosome 9p21 in various ethnic groups might be different, replication is needed to confirm the potential effects of chromosome 9p21 in other groups. In addition, genetic factors implicated in atherogenesis may affect the outcome of cardiovascular disease. However, little data is available regarding the impact of chromosome 9p21 on the prognosis of Asian patients with CAD. The present study was conducted to assess the association of rs1333049 polymorphism, one representative polymorphism on chromosome 9p21 (7), with MI, angiographic severity of CAD, and occurrence of major adverse cardiac events (MACE) after acute MI in Han Chinese.

Materials and methods

Study population

The study protocol was approved by the Hospitals Ethics Committee. All participants were of Chinese Han origin and gave written informed consent. There were 584 patients included in this study who survived a first acute ST-segment elevation MI between November 2003 and December 2006. MI was defined as 1) ischemic chest pain of $>$30 min duration not relieved by sublingual nitrates, 2) new ST-segment elevation in at least two contiguous leads of 12-lead electrocardiogram, with the cut-off points $\geq$0.2 mV, 3) new, or presumably new, left bundle branch block (LBBB), 4) increased serum creatine kinase MB and troponin T at least 2 times greater than the upper limit of the reference interval. To avoid confounding results, patients with concomitant severe kidney disease (12 patients), liver disease (13 patients), malignancy (2 patients), valvular disease (19 patients) and cardiomyopathy (3 patients) were excluded. Fifteen patients lost to follow-up were also excluded leaving 520 patients for inclusion in the analysis.

The control subjects were residents of three major districts in Shanghai who received an annual physical examination in 2005. A detailed medical and family history was obtained; none had documented CAD, severe kidney or liver disease, or malignancy. The control subjects were selected to match MI patients with respect to age, gender, and traditional risk factors such as smoking, diabetes and hypertension, without knowledge of chromosome 9p21 genotypes.

Coronary angiography was performed using standard Judkins technique or radial approach. Severity of CAD was defined according to the total number of significant stenotic coronary arteries (luminal diameter narrowing $\geq$50%). Coronary lesion types (A, B_1, B_2, or C) were defined according to a modified classification of the American College of Cardiology/ American Heart Association (11).

Two-dimensional echocardiography was performed at discharge using Vivid-7 system (GE Vingmed Sound AS, Horton, Norway). Left ventricular ejection fraction (LVEF) was determined using apical four chamber view by Simpson's method.

Patients with MI received clinical follow-up in a special outpatient clinic or were contacted by telephone every 3 months after initial angiography (mean, 29$\pm$15 months). Occurrence of MACE included cardiac death, recurrence of non-fatal MI, recurrent angina or heart failure requiring hospitalization. In order to guarantee quality of the data, cause of death was verified by reviewing hospital records and death certificates. All MACE were reviewed by two experienced interventional cardiologists.

Blood samples were collected after an overnight fast at hospital admission and stored at –80°C. White blood cell count, serum glucose, creatinine, and lipid profiles [total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), lipoprotein (a), apolipoprotein A (apoA), apolipoprotein B (apoB) and triglycerides] were measured (HITACHI 912 Analyzer, Roche Diagnostics, Germany).

Genotype determination

Whole blood was drawn from each participant and genomic DNA was extracted from peripheral blood leucocytes using standard phenol-chloroform extraction. Genotyping was performed with TaqMan single nucleotide polymorphism (SNP) allelic discrimination by means of an ABI 7900HT (Applied Biosystems, Foster City, CA, USA) in a 384-well format. The TaqMan Assay kit was purchased from Applied Biosystems (Foster City, CA, USA). Genotyping was performed in a 5-μL volume containing 2.5 μL of TaqMan Universal PCR Master Mix, 0.125 μL of 40$\times$ TaqMan MGB Assay Mix, and 25 ng of genomic DNA. Primers of rs1333049 polymorphism were TCACTACCCTACTGTCATTCCTCAT and TTGCfjTTACCTCTGCGAGTGG. Probes were VIC-CAACAGTTCAAAAGCA and FAM-AACAGTTGAAAAGCA. Primers of rs10757274 were CCCCCGTGGGTCAAATCTAAG and AGAATTCCCTACCCCTATCTCCTATCT. Probes were VIC-CTGAGTGTTGAGACATA and FAM-CTGAGTGTTGGGACATA. Data were analyzed using the ABI Prism SDS software version 2.1 (Applied Biosystems).

Statistical analysis

Continuous and categorical variables were expressed as mean$\pm$SD and frequencies, respectively. Differences among groups were assessed using the χ^2-test, Kruskal-Wallis H or ANOVA. The χ^2-test for goodness of fit was used to verify agreement with Hardy-Weinberg equilibrium. Cumulative survival plots according to the genotype were evaluated using univariately by Kaplan-Meier analysis (log-rank test). Multivariate logistic analysis was performed to determine independent factors for occurrence of MI. A 2-sided probability level of $\leq$0.05 was used for statistical significance. All analyses were done with SPSS for Windows 13.0 (SPSS Inc, Chicago, IL, USA).

Results

The genotype distribution in patients with MI and controls was in Hardy-Weinberg equilibrium (all $p>0.05$). In this study, we performed rs1333049 and rs10757274 genotypes in 250 control subjects and found they were in strong linkage disequilibrium ($r^2=0.92$). Therefore, rs1333049 was finally chosen in the study.

Clinical characteristics of the controls and patients with MI are shown in Table 1. Compared with controls, patients with MI had more traditional risk factors with higher fasting glucose, apoB, lipoprotein (a), and creatinine concentrations and lower apoA or HDL-C level (all $p<0.01$). No association of conventional risk factors with rs1333049 was observed in patients or controls.

Patients with MI had higher frequencies of the *CC* genotype (30.0% vs. 20.7%) or *C* allele (55.5% vs. 46.2%) compared with controls (all $p<0.01$) using univariate analysis (Table 1). Multivariate logistic regression analysis revealed that genotypes carrying allele *C* were independent risk factors for MI after adjustment for conventional risk factors [odds ratio (OR) 1.41, 95% confidence interval (CI) 1.17–1.70, $p<0.001$]. Body mass index (BMI), triglyceride, total cholesterol, low HDL-C, lipoprotein (a), and creatinine were also found to be independent determinants for MI (Table 2).

There was no significant difference in number of diseased coronary arteries, lesion morphology, infarct site, and stroke among the subgroups of rs1333049 genotype (Table 3). Also there was no difference in LVEF, incidence of recurrence of non-fatal MI, recurrent angina, heart failure requiring hospitalization or composite MACE among patients with varying genotypes (Table 4). Cumulative survival rate was also similar among the three genotypes (Figure 1).

Discussion

The present study demonstrated that rs1333049 polymorphism on chromosome 9p21 was associated with MI, but not with angiographic severity of CAD and 2 years occurrence of MACE after MI in Han Chinese.

The Wellcome Trust Case Control Consortium identified an association of rs1333049 polymorphism with CAD ($p<10^{-14}$) in Caucasians (6). A later meta-analysis revealed that genotypes carrying allele *C* were associated with an increase of 24% (95% CI=1.20–1.29) in risk for CAD. Our results showed that the OR of allele *C* for MI was 1.41 (95% CI 1.17–1.70) after adjusting for conventional risk

Table 1 Association of baseline characteristics with rs1333049 in controls and patients with MI.

Basic characteristics	Controls (n=560)	MI patients (n=520)	Controls			MI patients		
			GG (n=159)	*GC* (n=285)	*CC* (n=116)	*GG* (n=99)	*GC* (n=265)	*CC* (n=156)
Age, years	63±11	64±12	62±12	63±10	63±10	65±12	63±12	64±11
Male, %	75.4	78.7	73.0	77.5	73.3	78.8	78.9	78.2
BMI, kg/m^2	24.57±2.59	24.32±2.78	24.58±2.46	24.66±2.72	24.32±2.42	24.41±2.49	24.31±2.96	24.27±2.65
Smoking, %	60.5	59.6	34.0	39.3	50.0	40.4	40.8	42.9
Hypertension, %	60.5	60.0	64.2	61.1	54.3	58.6	62.3	55.8
Diabetes, %	40.0	41.3	22.6	20.0	13.8	21.2	21.9	17.3
Systolic blood pressure, mm Hg	133±18	129±21*	134±18	134±19	131±18	130±23	129±21	128±18
Diastolic blood pressure, mm Hg	82±12	78±12*	83±11	82±12	79±12	79±12	78±11	79±12
Triglyceride, mmol/L	1.88±1.56	1.85±1.16	1.92±1.67	1.88±1.38	1.85±1.80	1.70±0.93	1.94±1.20	1.79±1.22
Total cholesterol, mmol/L	4.62±0.99	4.60±1.04	4.63±1.03	4.66±0.95	4.50±1.06	4.57±0.94	4.63±1.10	4.57±1.0
HDL-C, mmol/L	1.30±0.47	1.09±0.24*	1.24±0.43	1.34±0.49	1.27±0.44	1.09±0.22	1.10±0.25	1.08±0.24
LDL-C, mmol/L	2.60±0.81	2.68±0.82	2.61±0.80	2.61±0.81	2.55±0.83	2.67±0.74	2.67±0.82	2.71±0.88
ApoA, g/L	1.31±0.26	1.21±0.18*	1.30±0.31	1.33±0.25	1.27±0.21	1.21±0.18	1.21±0.18	1.20±0.18
ApoB, g/L	0.88±0.22	0.92±0.23*	0.89±0.23	0.89±0.21	0.86±0.26	0.91±0.21	0.92±0.23	0.93±0.24
Lipoprotein (a), g/L	0.21±0.18	0.26±0.19*	0.22±0.16	0.21±0.21	0.20±0.13	0.27±0.17	0.26±0.21	0.26±0.17
Fasting glucose, mmol/L	5.53±1.63	5.87±1.83*	5.54±1.75	5.49±1.61	5.59±1.52	5.93±1.88	5.85±1.85	5.87±1.75
Creatinine, mg/L	83.59±18.46	92.94±30.97*	82.09±16.70	84.43±20.23	83.59±16.06	92.29±20.47	93.05±34.46	93.16±30.40
Uric acid, μmol/L	335.92±77.30	327.26±80.39	334.52±72.55	341.73±83.09	323.59±67.26	331.55±82.53	327.25±79.47	324.56±80.98
CC genotype of rs1333049, %	20.7	30.0*						
C allele of rs1333049, %	46.2	55.5*						
Hardy-Weinberg equilibrium	p=0.572	p=0.471						

Values are presented as mean±SD or percent. *p<0.05, MI patients vs. controls. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA, apolipoprotein A; apoB, apolipoprotein B; MI, myocardial infarction.

Table 2 Multivariate logistic regression analysis.

Risk factors	OR	p-Value	95% CI
BMI	0.93	0.006	0.89–0.98
Triglyceride	0.85	0.020	0.75–0.98
Total cholesterol	1.43	0.033	1.03–1.98
HDL-C	0.08	<0.001	0.05–0.15
LDL-C	0.86	0.432	0.60–1.25
Lipoprotein (a)	4.11	<0.001	1.91–8.83
Fasting glucose	1.04	0.281	0.97–1.12
Creatinine	1.02	<0.001	1.01–1.02
rs1333049 C allele	1.41	<0.001	1.17–1.70

OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

factors, indicating the possible impact of rs1333049 polymorphism on CAD in Chinese.

In this study, rs1333049 polymorphism was not associated with total number of diseased vessels or morphology of lesions. These observations were in line with the report by Anderson et al. (12), and suggested that variants at the 9p21 locus may robustly predict the prevalence of angiographic CAD, but not angiographic CAD severity. Assimes et al. revealed that chromosome 9p21 variation was associated with total coronary plaque burden as expressed by calcification scores (13). However, angiographic CAD severity defined as number of stenotic coronary arteries appeared to correlate weakly with atherosclerotic plaque burden of the coronary tree.

Several prospective studies have shown that chromosome 9p21 variation was associated with development of atherosclerosis and incident cardiovascular disease (14–16). However, Chen et al. revealed that 9p21 conferred null effects on the severity or progression of coronary atherosclerosis in Caucasians (17). Likewise, a recent report from the Rotterdam cohort study did not show an association of chromosome 9p21 with incidence of CAD or MI in older individuals (18). In our study, no association was observed between genotypes of rs1333049 polymorphism and occurrence of MACE after MI. These results suggest that the predictive value of chromosome 9p21 for clinical outcomes in these patients may not be sufficient, at least for Han Chinese. This

Table 3 Association of rs1333049 with severity of MI at baseline.

	GG (n=99)	*GC* (n=265)	*CC* (n=156)	p-Value
Number of diseased arteries				
≤1 vessel disease, %	42.4	37.7	32.1	
2 vessel disease, %	32.3	34.3	36.5	0.550
3 vessel disease, %	25.3	27.9	31.5	
Number of significant stenoses, n	120	308	185	0.322
Morphology of significant lesions				
Type A, %	12.5	17.9	14.1	
Type B1, %	31.7	33.8	30.3	
Type B2, %	37.5	35.9	34.6	0.221
Type C, %	18.3	12.4	21.1	
Echocardiography				
LVEF, %	56.3±9.1	57.5±8.1	56.5±9.3	0.608
Infarct site				
Anterior MI, %	34.3	35.8	34.0	0.916
Inferior MI, %	48.5	40.8	41.0	0.384
Anterior+inferior MI, %	12.1	17.0	16.7	0.447
Length of hospital stay, days	14±5	14±4	15±6	0.015
Anti-hypertension treatment, %	31.4	24.7	24.6	0.387
Statin treatment, %	5.9	9.5	9.1	0.536
Ischemic stroke history, %	13.1	11.3	10.3	0.780

Data are presented as mean±SD or percent. LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Table 4 Association of rs1333049 with clinical outcome after MI.

	GG (n=99)	*GC* (n=265)	*CC* (n=156)	p-Value
Treatment				
Primary PCI, %	78.8	80.0	85.3	0.314
Aspirin, %	90.9	94.3	91.7	0.410
ACEI or ARB, %	67.7	64.9	62.8	0.730
β-Blocker, %	45.5	49.1	48.7	0.822
Statins, %	54.5	56.2	51.6	0.657
Duration, months	28±18	30±17	29±17	0.685
Adverse events				
Rehospitalization, n	1±1	1±1	1±1	0.263
Death, %	2.0	1.1	2.6	0.537
Non-fatal MI, %	5.1	1.9	3.2	0.265
Combined MACE, %	48.8	49.7	51.2	0.940

Data are presented as mean±SD or percent. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutanous coronary intervention.

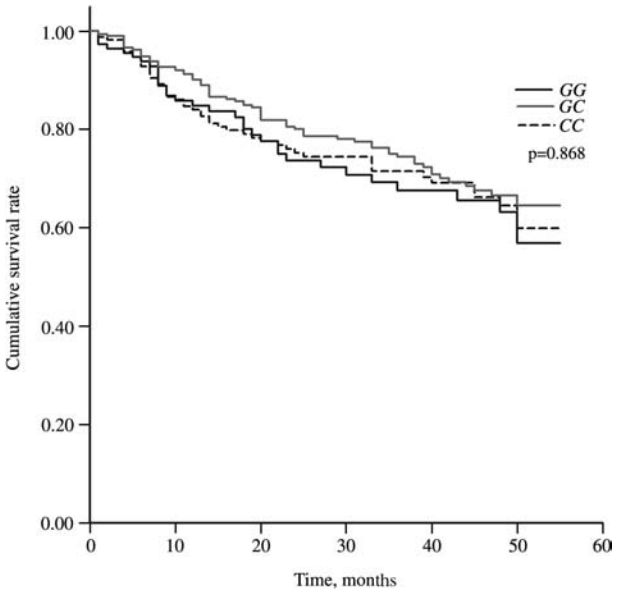

Figure 1 Kaplan-Meier survival plot by rs1333049. Cumulative survival rate was similar among the *GG* (n = 99), *GC* (n = 265), and *CC* (n = 156) genotypes.

may be explained by the lack of relation between chromosome 9p21 polymorphism and left ventricular function and severity of CAD; the latter two factors were major determinants for prognosis in patients with MI. Furthermore, medical or interventional therapy could mitigate the influence of certain genetic factors including rs1333049 polymorphism in cardiovascular disease. Finally, to a certain extent, optimizing lifestyle and proper control of risk factors would weaken the genetic impact on atherosclerosis at the individual level.

In multiple logistic regression analysis, we found that serum creatinine was associated with MI in addition to rs1333049. Renal impairment may be a marker for undiagnosed vascular disease or severity of vascular damage. It is also possible that atherogenic effects of traditional risk factors such as tobacco use, hyperlipidemia, hypertension, and diabetes may be greater in the presence of moderate to severe renal failure, which could also contribute to an increase in progression of CAD, MI and late mortality (19).

Some studies have probed the mechanisms behind the associative effect of chromosome 9p21. The locus on chromosome 9p21 spans about 50–60 kb, containing no protein coding gene. Nevertheless, existing nearby is a cluster cell cycle promoting factor genes including cyclin-dependent kinase inhibitors 2A and 2B (*CDKN2A* and *CDKN2B*). These play a significant role in regulating cell proliferation, senescence and apoptosis (20). It is possible that certain genetic variants in this region relate to the altered expression of *CDKN2A*, *CDKN2B*, and/or other genes located nearby (21, 22).

Conclusions

In summary, the rs1333049 polymorphisms on chromosome 9p21 were associated with MI, but not angiographic severity of CAD and did not affect MACE rate during a 2-year follow-up in Han Chinese. Further large studies are needed to clarify the role of the locus at chromosome 9p21 in atherosclerosis and its complications.

Conflicts of interest

We did not accept any funding or support from an organization that may in any way gain or lose financially from the results of our study or the conclusions of our review. We are not employed by an organization that may gain or lose financially from the results of our study or our conclusions. We have no other conflicts of interest.

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